

Intracuff alkalized lidocaine reduces sedative/analgesic requirements for mechanically ventilated patients

Ahmed Sobhy Basuni

Department of Anesthesiology and Intensive Care, Faculty of Medicine, Tanta University, Egypt

Address for correspondence:

Prof. Ahmed Sobhy Basuni,
Department of Anesthesiology and Intensive Care, Faculty of Medicine, Tanta University, Egypt.
E-mail: ahmed.basuni@med.tanta.edu.eg

ABSTRACT

Background: The objective of this study is to investigate the effect of intracuff alkalized lidocaine on sedative/analgesic requirements for mechanically ventilated patients and its consequence on patient-ventilator interaction. **Materials and Methods:** A total of 64 patients who expected to require ventilatory support for a period of more than 48 h were randomly assigned to groups S and L. In group S, the endotracheal tube (ETT) cuffs were inflated with normal saline. In group L, the ETT cuffs were inflated with lidocaine 2% and sodium bicarbonate 8.4%. The investigator and the surgical intensive care unit staff were blinded to the nature of cuff-filled solutions. Sedation was maintained with propofol and fentanyl infusions. The total requirements for propofol and fentanyl, frequency and severity of cough and number of ineffective triggering during the first 24 h of mechanical ventilation were recorded. **Results:** There was a significant reduction (about 30%) in the requirements for propofol and fentanyl in patients who received intracuff alkalized lidocaine; $P < 0.001$. The frequency and severity of cough were significantly lower in group L compared with group S and the frequency of ineffective triggering was significantly lower in group L; $P < 0.001$ for both comparisons. **Conclusion:** Intracuff alkalized lidocaine increases ETT tolerance and hence, decreases sedatives/analgesics requirements for mechanically ventilated patients. This results in improved patient-ventilator synchronization.

Key words: Endotracheal tube cuff irritation, endotracheal tube cuff tolerance, intracuff alkalized lidocaine

INTRODUCTION

Endotracheal tube (ETT) is a source of discomfort and pain in mechanically ventilated intensive care unit (ICU) patient who have to keep the ETT for a long time. Tracheal tube discomfort is primarily caused by cuff irritation that increases airway secretions and hence, exacerbates cough and produces more discomfort. To keep the patient in a comfortable state a significant amount of sedatives and analgesics are usually administered, particularly in the first few days, though their cumulative effect may increase ICU stay, morbidity and mortality. In addition, these drugs may decrease inspiratory

muscle efforts and increase patient-ventilator asynchrony, particularly ineffective triggering.^[1] Therefore, any strategy to decrease sedative/analgesic requirements is appreciated.

Using of lidocaine hydrochloride with or without addition of sodium bicarbonate (i.e., alkalization) for filling the cuff of ETT instead of air has been studied during general anesthesia.^[2-5] Intracuff alkalized lidocaine has been demonstrated to continuously diffuse across the cuff wall, anesthetize the underlying tracheal mucosa and thereby, reduce the ETT-induced emergence phenomena from general anesthesia, particularly, during surgery of long duration.^[3-5] The application of this technique in ICU patients has not been described previously, despite that it would seem logical in an attempt to improve ETT tolerance and thereby, to reduce the requirements for sedative/analgesic drugs. Therefore, the aim of the present study was to investigate the effect of intracuff alkalized lidocaine on sedative/analgesic requirements for ICU patients undergoing mechanical ventilation and the consequence of this technique on patient-ventilator interaction.

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MATERIALS AND METHODS

Institutional review board approval and written informed consent from patient's next of kin were obtained. The study was carried out in the Surgical Intensive Care Unit (SICU) of Tanta University Hospital during the period from October 2012 to June 2013. Patients who expected to require ventilatory support for a period of more than 48 h were consecutively enrolled in the study. The exclusion criteria were age <18 years, body mass index >35 kg/m², post-cardiac arrest, ventilation through tracheotomy, hemodynamic instability, in need for a positive end expiratory pressure (PEEP) ≥8 cm H₂O, excessive amount of respiratory secretions, brain injury and history of chronic obstructive pulmonary disease, cardiovascular, hepatic or renal disease. Patients were excluded from the study after enrollment, if ventilation was deemed ineffective without muscle relaxation.

Patients were randomly assigned to either group S (control group): The ETT cuffs were inflated with normal saline or group L (intervention group): The ETT cuffs were inflated with a mixture of lidocaine 2% (Xylocaine[®], AstraZeneca, Paris, France) and sodium bicarbonate (NaHCO₃) 8.4% (sodium bicarbonate 8.4%, Otsuka pharmaceutical Co., Egypt) at a ratio of 1:1 ml. Randomization was carried out according to a computer-generated random numbers table and syringes containing 10 ml of either saline or alkalinized lidocaine were prepared by the hospital pharmacy. The author and the SICU staff were blinded to the nature of syringes-filled solutions.

Oral endotracheal intubation was performed after administration of an IV bolus of propofol (Diprivan[®], Fresenius Kabi, Austria) 0.5-1.5 mg/kg and cisatracurium besylate (Nimbex, GlaxoSmithKline, Egypt) 0.5 mg/kg using an ETT tube (3TM, Zhejiang S. Medical Device Co., Ltd, China) 7-7.5 mm inner diameter for women and 7.5-8 mm inner diameter for men. The ETT cuffs (high volume-low pressure) were inflated with either saline or alkalinized lidocaine according to group assignment at the minimal occlusive volume (i.e., no leakage was detected under controlled ventilation). They were ventilated with eVent ventilator (eVent medical Ltd, Galway, Ireland) using pressure assisted control ventilation. Ventilatory settings were adjusted to obtain a tidal volume around 6-8 ml/kg delivered with inspiratory flow rate ≥60 L/min. Pressure triggering sensitivity was set between 5 and 1 cm H₂O, respiratory rate <30/min and PEEP to maintain PaO₂ >90 mmHg with a FiO₂ <0.6.

Sedation was maintained with baseline infusions of propofol 0.2-1 mg/kg/h to achieve a score of 3-4

on the sedation agitation scale (SAS)^[6] and fentanyl (Fentanyl, Hameln pharmaceutical GmbH, Germany) 25-100 µg/h to achieve a score of 0 on the behavioral pain scale (BPS).^[7] The levels of sedation and analgesia were monitored hourly. If at any time they were assessed to be outside the target levels, nurses achieved the target levels either by administering additional boluses of either propofol 10 mg or fentanyl 25 µg or by altering the infusion rates. Reversible causes of anxiety and agitation including needing explanations/reassurance, excessive light or sounds and airway obstruction were continuously excluded before altering the infusion rates.

During the first 24 h of mechanical ventilation, total requirements for propofol and fentanyl were recorded. The episodes of coughing not related to endotracheal suctioning were counted and evaluated according to a three points scale (1: Mild, 2: Moderate and 3: Severe). The ventilator airway pressure-time and flow-time waveforms were captured downloaded and enlarged for counting the numbers of ineffective triggering; defined as a simultaneous decrease in airway pressure and an increase in airflow without assisted cycle.^[8]

Statistics

The primary endpoint was the total requirements for propofol and fentanyl in the first 24 h of mechanical ventilation. A total of 25 patients were required per group to determine that inflation of the ETT cuff with alkalinized lidocaine would reduce the sedative/analgesic requirements by 35% based on a previous study by Mallick *et al.*,^[9] with 95% power ($\alpha = 0.05$). 32 patients were included per group after calculation of a dropout rate of 25%. Data were analyzed using SPSS (version 20) and are presented as mean ± SD or number (%) as appropriate. After testing data distribution, unpaired Student's *t*-test was used for comparison of parametric data between groups. Non-parametric data (patients' sex, primary diagnosis, survival and severity of cough) were assessed using Kruskal-Wallis test. A *P* < 0.05 was considered to be statistically significant.

RESULTS

A total number of 64 patients of both sexes were recruited in the study. 14 patients were excluded from subsequent analysis: 3 patients in group S were transferred to another hospital and 11 patients (5 patients in group S and 6 patients in group L) required neuromuscular block during the study period because of deterioration of oxygenation. A total of 24 patients remained in group S and 26 patients in group L [Figure 1].

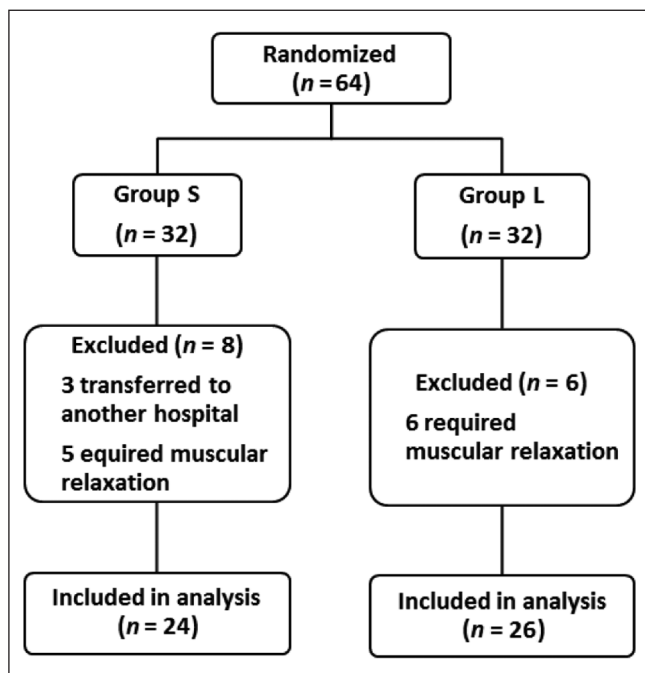


Figure 1: Trail profile

Patients’ data were comparable in both groups; $P > 0.05$ [Table 1]. They had no significant organ dysfunction except respiratory failure. All patients were tracheally intubated at the first attempt. No cuff ruptures or problems were encountered during endotracheal intubation and there was no difference in the volume of solutions injected into the cuff between groups (7.9 ± 1.9 for the saline group and 6.8 ± 2.4 ml for the alkalinized lidocaine group; $P > 0.05$).

During the first 24 h of mechanical ventilation, there was a significant reduction of about 30% in the requirements for propofol and fentanyl in patients who received intracuff alkalinized lidocaine; $P < 0.001$. The frequency and severity of cough were significantly lower in group L compared with group S and the frequency of ineffective triggering was significantly lower in group L; $P < 0.001$ for both comparisons [Table 2].

Patients in group L appeared to be less bothered by pulmonary suctioning compared with those of group S; they developed less cough and restlessness in response to tracheal suctioning. Although blood pressure and heart rate were not of the studied parameters, fewer episodes of hypertension and tachycardia were observed in the alkalinized lidocaine.

DISCUSSION

The present study demonstrated a significant reduction in the total requirements for propofol and fentanyl and lowering of the frequency and severity of cough in the intervention group than the control group. In other words,

Table 1: Patients’ data

Variable	Group S (n = 24)	Group L (n = 26)
Age, year	48.75±10.41	49.15±10.54
Weight, kg	83.65±8.94	84.84±10.16
Sex, M/F	14/10	13/13
APACHE II score	15±4	18±2
SOFA	6±3	8±2
Primary diagnosis, n (%)		
Pneumonia	7 (29)	9 (35)
Peritonitis	8 (33)	9 (35)
Pancreatitis	5 (21)	4 (15)
Massive blood transfusion	4 (17)	4 (15)
HR, /min	99.1±13.3	100.7±16.6
MAP, mmHg	52.7±9.40	56.1±8.78
CVP, cmH ₂ O	10±2	11±1
RR, /min	23±3	21±2
pH	7.26±0.06	7.29±0.13
SaO ₂	84.6±0.87	81.3±1.22
PaO ₂ , mmHg	59.3±7.60	53±11.22
PaCO ₂ , mmHg	29.3±3.26	28.2±5.61
PaO ₂ /FiO ₂	183.2±44	193.2±51
V _T , ml	501±46	460±55
P _{aw} , cmH ₂ O	23±4	26±5
P _{mean} , cmH ₂ O	9±3	10±2
P _{plat} , cmH ₂ O	26±5	28±6
PEEP, cmH ₂ O	6±2	6±1
Duration of ventilation, day	5±2	4±3
ICU stay, day	10±3	9±2
Survival, n (%)	18 (75)	16 (62)

APACHE II score: Acute physiology and chronic health evaluation II score; SOFA: Sequential organ failure assessment. HR: Heart rate; MAP: Mean arterial pressure; CVP: Central venous pressure; RR: Respiratory rate; pH; SaO₂: Oxygen saturation; PaO₂: Arterial oxygen tension; PaCO₂: Arterial carbon dioxide tension were recorded immediately before mechanical ventilation; SaO₂ and PaO₂ were obtained at FiO₂ (inspired oxygen fraction) = 40%; V_T: Tidal volume; P_{aw}: Peak airway pressure; P_{mean}: Mean airway pressure; P_{plat}: Plateau pressure; PEEP: Positive end expiratory pressure; ICU: Intensive care unit

Table 2: Propofol and fentanyl requirements, frequency and severity of cough, frequency of ineffective triggering during the 24 h of the study in both groups

Variable	Group S (n = 24)	Group L (n = 26)	P value
Propofol, mg	1743±438	1392±512	0.001
Fentanyl, µg	784±226	593±341	0.001
Cough, n	22±5	12±7	0.001
Mild cough %	23	76	0.034
Moderate cough %	49	24	
Severe cough %	28	0	
Ineffective triggering, n	4320±672	2880±553	0.001

intracuff alkalinized lidocaine increased ETT tolerance. Furthermore, intracuff alkalinized lidocaine reduced the frequency of ineffective triggering.

Consistent with the current results, Hirota *et al.* reported that inflation of the tracheostomy tube cuff with

5 ml lidocaine (4%) solution significantly reduced tube discomfort in patients undergoing tracheostomy following oral cancer resection as evaluated by a visual analogue scale.^[10] In other studies, instillation of lidocaine onto tracheal mucosa reduced post-extubation cough on the emergence from general anesthesia^[11] and requirements of sedative/analgesic in artificially ventilated patients.^[9] This technique was limited by incomplete effectiveness in controlling of cough reflex as the ETT cuff shields underlying mucosa from exposure to instilled lidocaine, possible bronchospasm due to mucosal stimulation from lidocaine instillation and need for special ETT (laser-driven in-tube accelerator [LITA] tube; laryngotracheal instillation of local anesthetic).^[11] Intracuff lidocaine has been shown to overcome the problems experienced with the LITA tube.^[12-15] However, a recent study failed to demonstrate the effectiveness of intracuff non-alkalinized 4% lidocaine in reducing coughing during emergence from general anesthesia in smokers.^[16]

The ETT cuff is manufactured from a thin semipermeable hydrophobic polyvinyl chloride membrane that allows slow diffusion of lidocaine and blocking of nociceptive stimuli (i.e., irritant and stretch stimuli) caused by the ETT and its cuff.^[14] Alkalization of lidocaine allowed for quicker and more efficient diffusion and hence use of small doses of lidocaine (40 mg).^[3-5] It has been shown, *in vitro*, that variations in volume and concentration of NaHCO₃ injected into the cuff had no effect on the diffusion of lidocaine.^[3,5] However, the lidocaine: NaHCO₃ (8.4%) ratio (1:1 ml) used in the present study has been shown to result in earlier reduction of anesthesia and spontaneous ventilation at the end of surgery, less cough and restlessness before suctioning and extubation and marked reduction in post-extubation sore throat during the first post-operative day.^[5]

Lidocaine is known to be absorbed rapidly from the tracheobronchial mucosa. However, for systemic lidocaine to be effective in reducing ETT discomfort a very higher maximal plasma concentration of lidocaine is required (IV lidocaine 2 mg/kg gives plasma lidocaine levels >3 µg/ml)^[17] than that attained in case of lidocaine diffusion with 8.4% NaHCO₃ (<0.08 µg/ml),^[3,4,18] suggesting that improved ETT tolerance after intracuff alkalized lidocaine is a local rather than a systemic effect.

Ineffective triggering occurs when patient's effort fails to drop airway pressure below ventilator trigger sensitivity. Though ineffective triggering results mainly from improper ventilatory settings (e.g. inappropriate trigger sensitivity) or abnormal pulmonary mechanics,^[1,19] sedatives and analgesics have been shown to depress the inspiratory drive and decrease the inspiratory muscle effort and thus increase ineffective triggering.^[20,21] In the present study, all

patients had acute lung injury/acute respiratory distress syndrome and hence, presumably comparable pulmonary mechanics; also, they were set on low trigger sensitivities (from -5 to -1 cm H₂O). Therefore, it is not surprising that the significant difference in frequency of ineffective triggering may be attributed to the difference in sedative/analgesic requirements.^[11,20] However, the reduction of ineffective triggering may be, partly, attributed to increased ETT tolerance and patient's comfort associated with intracuff alkalized lidocaine.

Monitoring of sedation and analgesia in ICU is inexact. However, the SAS is one of the most valid and reliable tools for assessment of quality and depth of sedation in adult ICU patients.^[6] Similarly, the BPS is a valid and reliable tool for assessment of pain.^[7]

Saline may not be a true control. Singh *et al.* reported that use of saline or 2% of lidocaine without alkalization as liquid media for filling the ETT cuff reduced post-extubation reactions.^[22] However, it was reasonable to use saline as a control as otherwise it would have been difficult to carry out the study in a blinded fashion.

The total dose of lidocaine 68 ± 24 mg over 24 h in this study (the mean volume used per ETT was 6.8 ± 2.4 ml i.e., 3.4 ± 1.2 ml of 2% lidocaine) is markedly smaller than the lidocaine doses used in the previous studies,^[12-15] and it is unlikely that toxicity would occur given the dose and duration of this study. On the other hand, lidocaine and NaHCO₃ mixture could be irritative if a cuff ruptures. However, *in vitro* and *in vivo* studies showed no cuff rupture or obstruction,^[5,12-15] which in agreement with the current results. Conversely, some cases of cuff rupture have been reported when lidocaine was used as lubricant or for local anesthesia.^[23]

CONCLUSION

Intracuff alkalized lidocaine improves ETT tolerance leading to reduction of sedatives and analgesic requirements for mechanically ventilated patients and improvement of patient-ventilator synchronization. This technique offers advantages for patients with cardiovascular disease, intracranial or intraocular hypertension or hyperactive pulmonary disease. Local anesthetics with longer duration of action (e.g. levobupivacaine) may be beneficial, but their safety and efficacy should be investigated.

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